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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,336	03/23/2004	Jacques Jolivet	STROMIX-0008 (PHARMA-357)	2203

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MILLEN, WHITE, ZELANO & BRANIGAN, PC
2200 CLARENDON BLVD
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
PURDY, KYLE A	

ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,336	JOLIVET ET AL.	
	Examiner	Art Unit	
	Kyle Purdy	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/30/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15 and 17-60* is/are pending in the application.

4a) Of the above claim(s) *3,17,39-42,48 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-15,18-38,43-47,49-53 and 55-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election Acknowledged

1. Applicant's election with traverse the species of A) leukemia and B) gemcitabine encompassing claims 1, 4-15, 18-38, 43-47, 49-53 and 55-60 in the reply filed on 5/19/2010 is acknowledged. The traversal is on the ground(s) that several actions have already been issued, and therefore there is no burden. The Examiner acknowledges the previous actions but cannot agree that the previous actions would preclude an election of species. Although the previous Examiner may not have found it a burden, the current Examiner, upon inheriting the case, felt a serious burden to perform a thorough search and examination. Moreover, the current Examiner cannot comment on what the previous Examiners view of a burden was, but the current Examiner felt a burden was present due to the large number of distinct diseases being claimed as well as 'further comprising' drugs. MPEP 811 states that while restriction should normally be performed before any action upon the merits, "it may be made at any time before final action" and that the Examiner should make a proper requirement "as early as possible in the prosecution."

2. The requirement is still deemed proper and is therefore made FINAL.

Status of Application

3. Claims 1, 3-15 and 17-60 are pending, claims 3, 17, 39-42, 48 and 54 are withdrawn as being directed to nonelected subject matter and claims 1, 4-15 and 18-38, 43-47, 49-53 and 55-60 are presented for examination on the merits. The following rejections are made.

Response to Applicants' Arguments

4. Applicants arguments filed 11/30/2009 regarding the rejection of claims 47 and 58 made by the Examiner under 35 USC 103(a) over De Bono et al. ((J. Clin. Oncol. 2002: 20(1): 96-109, abstract) in view of Lokich et al. (Ann Oncol. 1997;8(1):15-25) have been fully considered and they are found persuasive. This rejection is withdrawn.

5. Applicants arguments filed 11/30/2009 regarding the rejection of claims 1, 3-15, 17-38, 48-56 and 58-60 made by the Examiner under 35 USC 103(a) over De Bono in view of Lokich, in further view of Chu et al. (US 5817667) have been fully considered and they are found persuasive. This rejection is withdrawn. It's noted that claims 3, 17, 48 and 54 are now withdrawn.

6. Applicants arguments filed 11/30/2009 regarding the rejection of claim 39 made by the Examiner under 35 USC 103(a) over De Bono in view of Lokich in further view of Chue and Schwartz et al. (US 6444638) have been fully considered and they are found persuasive. This rejection is withdrawn.

7. All previous obviousness-type double patenting rejections have been withdrawn.

New Rejections
Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

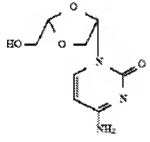
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. **Claims 1, 6-12, 23-28, 36, 37, 47, 51, 52, 58 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chu et al. (US 5817667; of record) in view of Lokich et al. (Ann. Oncology, 1997, 8(1), 15-25; of record) and Siu et al. (Ann. Oncology, 1998, 9, 885-891).**

12. Chu is directed to methods of using the compound (-)-OddC (aka troxacitabine ('OddC herein)) which has the formula  . OddC is taught to be active against

various cancer cells such as leukemia and exhibits low toxicity toward healthy cells in the host (see column 3, lines 45-50). Preferred plasma concentrations range from 0.01 uM to 30 mM (see column 11, line 15). OddC may be administered intravenously. OddC may also be administered together with another active agent.

13. Chu fails to teach continuous infusion over a 72 hour period wherein a stead state OddC plasma concentration of 0.03-2.0 uM is reached. Chu fails to teach repeating the continuous infusion every 4 weeks.

14. Lokich teaches that some anti-neoplastic agents are administered as a continuous 24-hours infusion for five or more days routinely, such as 5-fluorouracil and cladrabine, while some agents, for example, fludarabine and etoposide are administered as a daily bolus for three to five days. The rationale for infusional administration for chemotherapeutic agents is generally based upon observing schedule dependency in experimental systems and drug pharmacology in which a short plasma half-life following bolus administration would limit tumor cell exposure; the infusion schedule may also mitigate the acute and chronic toxicities commonly associated with high peak levels (see page 18, Table 3). Lokich teach that infusional schedules employ various durations of administration including 24-hour infusion repeated at weekly or longer intervals; 96-120 hour infusions; 7 or 14 day infusions; and protracted infusion for weeks or months (see page 15, left column).

15. Siu is directed to using (-)-2'-deoxy-3'-oxacytidine (BCH-4556) (aka troxactibane/OddC) against human tumor colony-forming units. OddC was provided either as a 1-hour exposure or continuously for up to two weeks. It's taught that the potency of OddC was greater with continuous exposure as compared to short-term exposure (see page 888, left

column). Moreover, it's taught that the IC_{50} for OddC against leukemia cells is between 0.024 and 0.11 uM (see page 900. left column). Other leukemia's have an OddC IC_{50} of 0.054, 0.0074 and 0.061 uM (see page 889, right column).

16. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Chu, Lokich and Siu with a reasonable expectation for success in arriving at a method of treating a cancer with Oddc wherein a steady state plasma concentration of between 0.03-2.0 uM is reached. The instantly claimed active agent was well known at the time the invention was filed. With respect to limitations of continuous exposure and steady state plasma concentrations, these are both obvious. Exposing patients continuously to chemotherapeutic agents for prolonged periods of time is routine in the art, especially when the agent is well tolerated (see Lokcih) as OddC is taught to be (see Chu). Further, the notion of continuous exposure to Oddc is taught by Siu. Siu exposes cancer cells to Oddc either continuously or acutely (i.e. short term). It's found that continuous exposure provides greater treatment results than acute treatment (see Table 2). There are therefore at least two significant reasons for continuous exposure A) OddC is well tolerated and can be continuously provided and B) better treatment results than acute exposure. The claimed plasma levels are also obvious. Siu gives multiple IC_{50} values of OddC against leukemia cells. These values include 0.024, 0.11, 0.054, 0.0074 and 0.061 uM. It's noted that the highest IC_{50} is 0.11 uM. Thus, one would have been motivated to provide OddC to a patient in such a way that the steady state plasma values were at or around these IC_{50} values to ensure that the cancerous cells would quickly die and the patient could recover. Any ordinary person would envisage repeating the infusion until the cancer died and would have endeavored to optimize the time in between

Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

17. **Claims 4, 5, 13-15, 18-22, 29-32, 38, 43-46, 49, 50, 53, 55-57 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chu et al. (US 5817667; of record) in view of Lokich et al. (Ann. Oncology, 1997, 8(1), 15-25; of record) and Siu et al. (Ann. Oncology, 1998, 9, 885-891) as applied to claims 1, 6-12, 23-28, 36, 37, 47, 51, 52, 58 and 59 above, and further in view of Giles et al. (US 6800639; filed 03/25/2002).**

18. Chu, Lokich and Siu fail to teach providing OddC together with gemcitabine and the daily dose rate of Oddc as being at a dose of 0.72-12.5 mg/m^2/day.

19. Giles is directed to treating cancers with a compound of the following formula:

wherein the preferred species is where R is H and B is cytosine (i.e. troxacitabine/OddC) (see column 3, lines 35-45). It's taught that the species is useful for treating leukemia such as chronic myelogenous leukemia (see column 9, lines 35-40). The agent may be used in conjunction with another nucleoside chemotherapeutic such as gemcitabine (see column 10, line 20). It's taught that agents may be administered by continuous infusion. And, ideally, the agent should be administered at a dose between about 1 mg/m^2 and about 8 mg/m^2 (see column 10, line 20). During continuous infusion however the dose should be titrated out at a rate of between 0.01 to about 5.0 mg/kg/hour (see column 10, lines 60-65). Giles also teaches that OddC

and gemcitabine may be administered either sequentially or simultaneously in separate or combine pharmaceutical vehicles (see column 4, lines 60).

20. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Chu, Lokich, Siu and Giles with a reasonable expectation for success in arriving at a method of treating a cancer with Oddc by administering a dose of 0.72-12.5 mg/m^2/day and where OddC is provided in a co-therapy with gemcitabine. With respect to the daily dose, this is obvious as Giles teaches that the preferred dose of OddC is about 1 to about 8 mg/m^2. If the art recognizes that an agent can be administered for a purpose (e.g. treating leukemia) at a given dose, then any person would have been motivated to employ a value from within that dosage range with a reasonable expectation that the method would achieve the results of the reference. Moreover, the range taught by Giles is encompassed entirely by the instantly claimed range, and thus if one were to pick the end points of the daily dose, then this would read directly on Applicants'' claim. See MPEP 2144. The notion of combing Oddc with gemcitabine is obvious, especially in view of Giles specifically teaching such. It would not have taken a great leap of technical skill to combine Chu and Giles and arrive at a method as is currently being claimed. As such, the combination of OddC and gemcitabine is nothing more than the result of common sense and ordinary skill. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

21. **Claims 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chu et al. (US 5817667; of record) in view of Lokich et al. (Ann. Oncology, 1997, 8(1), 15-25; of**

record) and Siu et al. (Ann. Oncology, 1998, 9, 885-891) as applied to claims 1, 6-12, 23-28, 36, 37, 47, 51, 52, 58 and 59 above, and further in view of Stevenson et al. (Euro. J. Cancer, 1998, 34, 1358-1362).

22. Chu, Lokich and Siu fail to teach repeating the continuous infusion in an interval of every 3 or 4 or 5 weeks.

23. Stevenson is directed to administering topotecan for a 21-day continuous infusion in patients with cancer. The 21-day continuous infusions were repeated every 28 days (see abstract).

24. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Chu, Lokich, Siu and Stevenson with a reasonable expectation for success in arriving at a method of providing a continuous infusion wherein the infusion procedure is repeated every several weeks. It would have been obvious to modify the prior art such that the continuous infusion of OddC would be repeated at some odd number of weeks, as taught Stevenson, in order to better treat the disease and not build a resistance to the active compound. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

Nonstatutory Obviousness-Type Double-Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

25. **Claims 1, 3-15, 17-38, 43-60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the following: claims 1-3, 9-10, 14-24, 30-36 of US Patent 6,630,480 in view of Lokich et al. (Ann. Oncol. 1997;8(1):15-25; of record) and Chu et al. (US Patent 5817667; of record).**

26. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are obvious variants of each other for essentially the same reasons stated above.

27. In particular, reference claim 1 is directed to a method for treating acute myelogenous leukemia or chronic myelogenous leukemia in a patient comprising a compound, including the identical instantly claimed compound and the instant claims are also directed to treating patients with leukemia. It is also noted that the dosage amount recited in reference claim 33 overlaps with the claimed dosage amount recited in instant claim 14.

28. Unlike the instant claims, the reference claims do not claim the instant claimed continuous infusion, period of continuous infusion, or the steady state plasma levels.

29. The above discussions of Lokich et al and Chu et al. are incorporated.

30. However, it would have been obvious to a person of skill in art to modify the reference method to arrive at the instant claimed invention in order to minimize the side effects of troxacitabine. One would have been motivated to do so9 because Chu teaches methods of treatment comprising troxacitabine via continuous infusion, while Lokich suggests providing chemotherapeutic agents for prolonged periods of time via continuous infusion is concerned with infusional anti-cancer drugs. Thus, the reference claims are deemed to be obvious variants of the instant claims for the above reasons.

Conclusion

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kyle A. Purdy whose telephone number is 571-270-3504. The examiner can normally be reached from 9AM to 5PM.

32. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau, can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

33. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Kyle Purdy/
Examiner, Art Unit 1611
July 19, 2010

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611